Volume 11 • Number 3 • 2008
VALUE IN HEALTH

Duration of Antipsychotic Drug Therapy in Real-World Practice: A Comparison with CATIE Trial Results

Lei Chen, PhD,[1,2] Jeffrey S. McCombs, PhD,[1] Jinhee Park, CPhil[1,3]

[1]Department of Pharmaceutical Economics and Policy, School of Pharmacy, University of Southern California, Los Angeles, CA, USA; [2]Analysis Group, Inc., Boston, MA, USA; [3]Glaxo Smith-Kline, Reaseach Triangle Park, NC, USA

ABSTRACT

Background: Duration of drug therapy is a key measure of drug effectiveness in schizophrenia. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial found that only olanzapine achieved a longer time to all-cause-discontinuation (TTAD) than a standard therapy comparator. This study compares the TTAD achieved when using alternative antipsychotics to treat patients with schizophrenia in real-world practice settings.

Methods: A total of 219,504 episodes of antipsychotic therapy initiated in the years 2000 to 2002 were identified using data from the California Medicaid (Medi-Cal) program. To capture the full range of treatment scenarios facing clinicians, four episode types were included: restarting therapy using the drug used in the preceding episode; restarting therapy using a different medication (delayed switches); switching therapy without a break in therapy; and augmentation. TTAD and changes in therapy were analyzed using ordinary least squares and logistic regressions and Cox proportional hazards models.

Results: Atypical antipsychotics consistently achieved longer TTAD and reduced switching rates relative to conventional antipsychotics. Differences in TTAD favoring atypical antipsychotics were 13 to 15 days in restart episodes; 28 to 36 days for delayed switching episodes; 41 to 52 days in switching episodes; and 59 to 63 days for augmentation ($P < 0.0001$ for all estimates). Differences between the atypical antipsychotics were smaller than reported in other studies and may not be clinically significant.

Conclusions: This study confirms two results from the CATIE study: Patients with schizophrenia frequently do not achieve stable, long-term drug therapy regardless of the specific drug used, and olanzapine achieved longer TTAD than conventional drugs. However, this study also found that patients treated with risperidone and quetiapine also achieved longer TTAD than patients treated with conventional antipsychotics.

Keywords: antipsychotic drugs, duration of therapy, switching.

Background

The use of atypical antipsychotics is coming under increased scrutiny as the cost for these medications has stressed the budgets of health systems, especially state Medicaid programs [1]. In response, the National Institute of Mental Health funded the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which implemented a hybrid study design that combined random assignment to alternative antipsychotics while attempting to mimic real-world practice. To date, the CATIE trial has reported three results of particular relevance to clinical practice [2–6]. First, the proportion of patients with 18 months of continuous therapy was unacceptably low, ranging from 18% for quetiapine to 36% for olanzapine. Second, only olanzapine achieved a significantly longer time-to-all-cause discontinuation than perphenazine, the conventional antipsychotic used as the comparison. Third, patients switching to olanzapine and risperidone in phase II of CATIE were found to achieve longer duration of therapy relative to quetiapine and ziprasidone. The median duration of therapy in phase I was 9.2 months for olanzapine; 5.6 months for perphenazine; 4.8 months for risperidone; and 4.6 months for quetiapine [2].

Several studies of patient compliance have found results that are generally consistent with CATIE [2–4]. Rascati et al. [7] compared olanzapine (n = 1906) and risperidone (n = 979) using Texas Medicaid data. Patients with schizophrenia newly started on olanzapine were less likely to discontinue treatment during the first year (8.89% vs. 14.51%, $P < 0.0001$) and had more days of therapy in the first year (248 days vs. 211 days, $P < 0.0001$) than risperidone patients. Gibson et al. [8] compared patients with schizophrenia using Michigan Medicaid data from 1996 to 1997. Patients initiating treatment with olanzapine (n = 458)

Address correspondence to: Jeffrey S. McCombs, Department of Pharmaceutical Economics and Policy, School of Pharmacy, University of Southern California, 1540 E. Alcazar St., Rm. CHP-140, Los Angeles, CA 90089-9004, USA. E-mail: jmccombs@usc.edu

10.1111/j.1524-4733.2007.00262.x

achieved a longer average duration of therapy (166 days) relative to risperidone patients (128 days, n = 481). Results from a multivariate Cox proportional hazards model found olanzapine patients to be 27% less likely to discontinue therapy (hazard ratio [HR] = 0.73, $P < 0.01$). Compliance with haloperidol was significantly worse relative to both olanzapine and risperidone. Ramsey et al. [9] evaluated Medicaid-only patients with schizophrenia who initiated monotherapy using olanzapine (n = 895), risperidone (n = 479), or haloperidol (n = 302) during the first 6 months of 1997. Olanzapine patients achieved longer duration of treatment than patients treated with either haloperidol (+69 days) or risperidone (+29 days, $P < 0.0001$ for both estimates). Using data from the Indiana Medicaid program, Zhao et al. [10] found significantly longer duration of therapy for olanzapine patients relative to both risperidone (+13 days) and quetiapine (+18 days, $P < 0.01$ for both estimates). Swartz et al. [11] compared olanzapine (n = 465), risperidone (n = 350), quetiapine (n = 178), and ziprasidone (n = 25) with oral conventional antipsychotics (n = 534) using data from the United States Schizophrenia Care and Assessment Program (US-SCAP) study. Unadjusted mean times to all-cause discontinuation were 303 days for clozapine, 266 days for olanzapine, 244 days for risperidone, 232 days for quetiapine, 216 days for ziprasidone, 218 for perphenazine, and 179 days for combination therapy of haloperidol and anticholinergic medications. These relative differences were confirmed by Cox proportional hazards models. Finally, Haro et al. [12] reported the 24 months results for monotherapy patients included in the Pan-European Schizophrenia Outpatient Health Outcomes Study. Fewer patients treated with olanzapine discontinued therapy at 2 years (23%, n = 3701) compared with risperidone (33%, n = 1362), quetiapine (49%, n = 545), or typical antipsychotics (44%, n = 499).

The antipsychotic treatment episodes included in the CATIE trial and in previous studies using retrospective database analyses do not represent the full range of patients who may initiate antipsychotic drug therapy. For example, Rosenheck et al. [5] caution their readers that the CATIE results cannot be generalized to first-episode patients, refractory patients, the elderly, patients with unstable medical problems, patients in nursing homes, or patients who wish to restart therapy using a medication used previously. The purpose of this article is to use data from the California Medicaid (Medi-Cal) program to investigate the drug therapy outcomes achieved across alternative antipsychotics under a wider range of clinical scenarios excluded for previous research. The patient's antipsychotic drug use history and current use at the time of treatment initiation were derived from the patient's prescription drug claims over a 10-year period between 1994 and 2003. These data were then used to define five episode types that reflect time off treatment, if any, and the antipsychotic medications used during the patient's prior treatment attempt. These five episode types are: the patient's first-observed MediCal-funded treatment attempt; patients restarting therapy with a medication used in their most recent treatment attempt; patients switching therapies after a period of no drug therapy; patients switching drugs with no break in treatment; and patients augmenting a pre-existing antipsychotic drug regimen. Previous research either required extended washout periods or combined a mix of episode types into a single sample. As patient compliance and drug selection could vary significantly across episode types (drug history), analyses that aggregate episode types into a single sample could be biased.

This study evaluates multiple measures of drug therapy outcomes: the likelihood of achieving 1 year of continuous therapy, days of continuous therapy, and the likelihood of changing therapies using prescription drug claims. Several studies have established that measures of adherence based on prescription drug claims are highly correlated with methods commonly used in clinical trials. For example, Choo et al. [13] found that pharmacy records correlated well with pill counts in terms of cumulative exposure and gaps in therapy over time, although neither measure correlated well with patient adherence with the timing of prescribed doses. Grymonpre et al. [14] found significant concordance between pill counts and pharmacy data in the elderly.

Methods

Data

A 100% sample of de-identified paid claims data from the fee-for-service portion of the Medi-Cal program for the period 1994 to 2003 was available for this analysis. Patients were eligible for inclusion in the study if they had a diagnosis of schizophrenia recorded on a paid claim (ICD-9 code 295.xx) and filled at least one prescription for an antipsychotic medication during the period. A limited number of additional exclusion criteria were applied once the drug use patterns of these patients were summarized into episodes of antipsychotic drug therapy. The research protocol was approved by the institutional review board at the University of Southern California.

Summary prescription drug data were created for each antipsychotic medication used by the patient over the entire 10-year data period. These data included the drug used, number of pills dispensed, days supply, and the number of days between prescriptions. Data for "days supply" were missing on a small percentage of prescription claims (less than 5%) and were replaced with the average days supply recorded for each

medication, usually a value very close to 30 days given the predominance of monthly prescriptions under Medi-Cal.

Unit of Analysis

An episode of antipsychotic drug therapy was defined each time a patient initiated treatment using an antipsychotic not used previously or restarted a medication after a break in therapy in excess of 15 days. The 15-day gap definition was selected in collaboration with the Medi-Cal program and reflects the findings of Weiden et al. [15], who used Medi-Cal data to document that the risk of hospitalization increased significantly in patients with schizophrenia after breaks in therapy as short as 10 days. Analysts with the Medi-Cal program agreed with the authors that allowing for longer gaps in therapy would risk missing the association between rapid destabilization of noncompliant patients with short-term breaks in therapy. Unfortunately, it is not possible to test the sensitivity of our study results to alternative gap definitions without creating a parallel data set summarizing all episodes of antipsychotic therapy over the entire 10-year period for all Medi-Cal patients with a diagnosis of schizophrenia using an alternative gap definition.

Five types of treatment episodes were identified using prescription drug data, four of which were included in this analysis:

First observed episode. By definition, each patient has one "first" episode of antipsychotic drug therapy recorded in the Medi-Cal paid claims file.

Restart episodes using the same medication. Restart episodes were defined if the patient was not on active antipsychotic drug therapy of any type for at least 15 days and initiated therapy with a medication used in their most recent prior treatment attempt. That is, these patients are using a specific antipsychotic intermittently without using any alternative products. A break in treatment was identified whenever a gap in drug therapy in excess of 15 days was observed based on days supply and refill dates for all antipsychotic medications used by the patient.

Delayed switches in drug therapy. Delayed switching episodes were defined if the patient changed therapy from the drugs used in their most recent prior treatment attempt, but after a break in the use of any antipsychotic therapy of at least 15 days.

Switching episodes. A switching episode was defined if a patient changed medication while still on active therapy or within 15 days of terminating a previous episode, and discontinued use of all previous medications within 60 days after starting his or her new therapy.

Augmentation episodes. An augmentation episode was defined when a patient changed therapies without a break in therapy and continued to purchase one or more of their previous medications beyond 60 days.

There will be overlapping episodes of drug use for both switching and augmentation episodes and these patients will enter the analysis twice, but possibly for different episode types. For example, if a patient restarts on Drug A, then augments with Drug B, then the patient will have a restart and augmentation episode sharing a period of drug use. Similarly, while restart and delayed switching episodes have no overlapping periods of drug use prior to treatment can still share overlapping post-treatment periods of drug use (i.e., a restart episode and augmentation episode for a patient initiated within 1 year). This is not, however, an important issue in this study of drug therapy outcomes, which are measured as days of continuous therapy on both the initial medication used at the start of the episode and on all subsequent antipsychotic medications started without a break in therapy.

The range of episode types outlined above includes virtually all patient attempts to use antipsychotic medications. This approach includes clinical scenarios not typically allowed into randomized clinical trials, such as patients switching therapies without a "washout" period and augmentation episodes. This approach also allows the analysis to compare across alternative medications while controlling for the treatment history of the patient. The CATIE investigators also recognized the importance of treatment history on compliance in their analysis of patients in phase I who were randomly assigned back onto the antipsychotic used previously [8]. Treatment history data are also used as independent variables in the statistical models to control treatment selection bias.

Separate analyses are conducted by episode type as the use of alternative drugs may vary significantly by episode type. Episode-specific analyses provide more complete and relevant information for clinicians who must select between alternative therapies across a wide range of clinical scenarios. This approach also avoids any confounding that may occur if the frequency of use of these medications differs across episode type and duration of therapy and switching rates differ significantly by type of episode. Previous research either excluded restarting, switching, and augmentation episodes or mixed episode types into a single sample, thus creating a potential bias against medications used more frequently in short-duration episode types.

Four additional selection criteria were applied once all episodes of treatment initiated by the patient over the entire 10-year data period were abstracted from the data. First, the first observed episode was dropped for all patients because of truncation of the data which prevented determination of the patient's

drug history at the start of treatment. For example, it is thought that a significant proportion of patients with schizophrenia qualified for Medicaid coverage at some point after their initial treatment attempt using an antipsychotic. Therefore, first observed episodes are likely to be a mix of episode types and were excluded from further analysis. Second, all episodes were screened for a minimum of 6 months of pretreatment data and 1-year (12 month) post-treatment data surrounding the month in which treatment was initiated. Third, this study was limited to episodes of drug therapy initiated after January 1, 2000 to insure that the "access effects" associated with the expansion of the Medi-Cal formulary in October 1997 had stabilized [16] and to avoid early quetiapine episodes as it received Food and Drug Administration approval in the fall of 1997. Finally, episodes of care initiated with either ziprasidone or clozapine were excluded from this analysis because of the limited sample size and the late availability of ziprasidone during the study period.

Statistical Methods

Compliance was measured as days of continuous therapy for both the index medication used in the treatment episode and across all medications used subsequently so long as there was no gap in drug availability in excess of 15 days. Other drug therapy outcomes include the time to the patient's use of an alternative antipsychotic not in use at the start of the episode. These time-to-switch data are then used to define dichotomous variables indicating that the patient switched or augmented their index medication within 1 year. Cox proportional hazards models were estimated for the time-to-termination and time-to-change in therapy. Logistic regression models were estimated for dichotomous outcome variables created if the time-to-termination or time-to-change in therapy was less than 360 days (i.e., within 1 year). Finally, ordinary least squares (OLS) regressions were estimated for duration of uninterrupted therapy.

The presence of multiple episodes for some patients violates the assumption of independence across observations. Under these conditions, the regression estimators continue to be unbiased; however, the estimated standard errors are biased. The heteroscedasticity-consistent matrix estimator developed by White [17] was used to adjust estimated standard errors for clustering of episode observations by patient, using procedures available in STATA [18].

Independent Variables

The development of an exhaustive list of independent variables is the first line of defense against treatment selection bias in nonrandomized studies that compare patient outcomes across alternative treatment options. This study has developed independent variables related to patient demographics, the diagnostic and psychotropic drug profile of the patient, and use of healthcare services in the 6 months before the episode's index date. Four prior use variables were created: three dichotomous variables indicating the use of acute hospital, psychiatric hospital, and nursing home services in the prior 6 months and the natural log of the total cost for all services with dates of service in the 6-month pretreatment period. Adjustment for missing Medicare payments were implemented based on methods used in previous research [16].

Antipsychotic drug use history variables include whether or not two antipsychotic medications were first purchased on the index date of the episode, the duration of therapy achieved during the patient's previous episode of therapy and the number of days between episodes (restart and delayed switching episodes), prior use of depot formulations, a dichotomous variable indicating whether or not the patient's new episode constituted a change in antipsychotic class (i.e., using an atypical antipsychotic after a treatment attempt with a conventional antipsychotic), and the average number of treatment attempts per year before the episode start date. This latter variable was created by maintaining a running count of episodes and then dividing this count by the total number of days of data available before each episode. The resulting "episodes per day" value was transformed into an annualized value by simply multiplying by 360 days.

Results

Baseline Patient Characteristics

The data on selected baseline characteristics of the study sample are presented in Table 1 by episode type and index drug. Several results point out the importance of breaking down comparisons of patient outcomes across drugs into separate analyses by episode type. First, the distributions of episode types are quite different across drugs. For example, olanzapine and risperidone are used primarily by patients restarting treatment, having used these drugs previously (61.5% and 57.6%, respectively). Only 38.8% of quetiapine episodes and 43.8% of episodes using typical antipsychotics are restart episodes. Second, the baseline characteristics of the patient sample changes significantly by episode type. For example, patients initiating an episode of augmentation therapy are more likely to be male, disabled, white, and more costly to treat in the prior 6 months than patients restarting a drug used previously. Aggregating different episode types into a single analysis could result in erroneous comparisons across drugs if episode type affects duration of therapy. Third, the average gap between restart episodes ranges from 56 days for quetiapine to 99 days for typical antipsychotics, far in excess of the minimum of 15-day gap used to define a break in therapy. The average gap

Table 1 Baseline patient characteristics by drug and type of episode

Demographics and prior use	Olanzapine	Risperidone	Quetiapine	Typicals
Restart episodes using same medication	N = 40,510 (61.5%)	N = 30,469 (57.6%)	N = 10,385 (38.3%)	N = 29,422 (43.8%)
Age (years)	42.5	43.5	42.0	46.3
White (%)	45.9	45.1	50.0	45.2
Male (%)	55.0	48.7	46.2	50.3
Disabled (%)	75.6	74.4	74.3	84.1
Health-care cost ($/prior 6 months)	6,674	6,677	7,930	5,454
Days off antipsychotic therapy	73	72	56	99
Delayed switching episodes	N = 11,459 (17.4%)	N = 9,483 (17.9%)	N = 6,407 (23.6%)	N = 11,176 (16.6%)
Age (years)	42.6	42.8	41.8	42.7
White (%)	47.7	46.7	48.7	46.7
Male (%)	54.2	50.1	50.1	51.7
Disabled (%)	77.3	75.6	75.6	79.8
Health-care cost ($/prior 6 months)	8,328	8,315	8,355	9,631
Days off antipsychotic therapy	314	305	240	236
Switching episodes	N = 7,694 (11.7%)	N = 6,761 (12.8%)	N = 5,258 (19.4%)	N = 7,055 (10.5%)
Age (years)	43.1	43.3	42.8	43.0
White (%)	52.7	52.0	54.5	51.1
Male (%)	52.5	49.8	47.9	50.6
Disabled (%)	80.2	79.7	78.1	82.2
Health-care cost ($/prior 6 months)	10,076	10,353	10,149	11,178
Augmentation episodes	N = 6181 (9.4%)	N = 6148 (11.6%)	N = 5091 (18.8%)	N = 19,510 (29.0%)
Age (in years)	42.9	42.8	42.1	43.7
White (%)	53.3	53.4	54.3	56.3
Male (%)	58.2	54.5	53.9	54.7
Disabled (%)	83.2	83.6	82.4	84.1
Health-care cost ($/prior 6 months)	10,209	10,767	10,472	14,558

between episodes for delayed switching episodes is even more dramatic, ranging between 236 days for conventional antipsychotics and 314 days for patients switching to olanzapine. These are the types of episodes that would be sensitive to an alternative definition of a break in therapy.

Descriptive Statistics: Drug Therapy Outcomes

The descriptive statistics describing the drug therapy outcomes achieved by patients using alternative antipsychotic medications are presented in Table 2. The pattern of unadjusted drug therapy outcomes across drugs is consistent across all episode types:

1. Patients initiating episodes of therapy using atypical antipsychotics achieve longer duration of treatment and are less likely to switch to other antipsychotics within 1 year.
2. The unadjusted results for patients initiating therapy using olanzapine are consistently better than those achieved by risperidone or quetiapine patients, although differences are small.
3. The range of unadjusted differences in duration across all four drugs is relatively small for patients restarting therapy on the drug used previously (14 days). The range of differences, however, becomes more significant when the patient is changing or augmenting therapy: 35 days for delayed switching episodes, 72 days for switching episodes, and 96 days for augmentation episodes.

These differences in the relative performance of alternative antipsychotics by episode type further underscore the importance of making head-to-head comparisons by episode type.

Multivariate Results

The OLS models of duration of therapy on the index antipsychotic are presented in Table 3 for all four episode types. Only those independent variables that were statistically significant in 3 of 4 analyses are listed because of space limitations. All three atypical antipsychotics were found to achieve significantly longer duration of therapy on the index medication for all types of episodes, ranging from 13 to 15 days in restart episodes to 59 to 65 days in augmentation episodes ($P < 0.0001$ for all estimates).

Several additional factors were found significantly to affect duration of therapy using the index medication. The patient's duration of therapy in their prior treatment episode was positively correlated with duration in the current episode, whereas the frequency of episodes per year is negatively correlated with persistence. The use of antidepressants and hypnotic medications in the 6 months before the episode are negatively correlated with duration of therapy, while mood stabilizer use is positively correlated with duration of therapy in 3 of 4 models. Duration of therapy generally improves with age but is negatively correlated with a prior psychiatric hospitalization and black

Table 2 Unadjusted medication use patterns by drug and type of episode

Medication use pattern	Olanzapine	Risperidone	Quetiapine	Typical antipsychotics
Restart episodes using same medication	N = 40,510	N = 30,469	N = 10,385	N = 29,422
Days of therapy: initial drug	142 (4.7 months)	139 (4.6 months)	135 (4.5 months)	128 (4.3 months)
Days of therapy: all drugs	157	155	156	154
Switch/augment (%)	12.58	12.38	19.11	15.11
Time to switch/augment	148	144	125	147
No. of additional APs in first year	2.13	2.15	2.41	2.43
Delayed switching episodes	N = 11,459	N = 9,483	N = 6,407	N = 11,176
Days of therapy: initial drug	143 (4.8 months)	135 (4.5 months)	127 (4.2 months)	108 (3.6 months)
Days of therapy: all drugs	177	170	166	159
Switch/augment (%)	26.93	27.23	31.14	33.94
Time to switch/augment	125	118	109	103
No. of additional APs in first year	2.46	2.41	2.70	2.91
Switching episodes	N = 7,694	N = 6,761	N = 5,258	N = 7,055
Days of therapy: initial drug	195 (6.5 months)	187 (6.2 months)	166 (5.5 months)	123 (4.1 months)
Days of therapy: all drugs	266	265	248	235
Switch/augment (%)	38.06	39.15	41.52	48.70
Time to switch/augment	65	64	68	47
No. of additional APs in first year	2.70	2.66	2.89	3.59
Augmentation episodes	N = 6,181	N = 6,148	N = 5,091	N = 19,510
Days of therapy: initial drug	186 (6.2 months)	179 (6.0 months)	162 (5.4 months)	90 (3.0 months)
Days of therapy: all drugs	363	364	343	377
Switch/augment (%)	39.82	41.23	41.64	51.14
Time to switch/augment	106	105	102	84
No. of additional APs in first year	2.64	2.62	2.79	3.29

AP, antipsychotics.

race. In general, duration of therapy is positively correlated with the patients' prior consumption of healthcare services as measured by the natural log of total cost.

The results for all analyses are summarized in Table 4 and are consistent with the unadjusted data presented in Table 2. Patients using olanzapine, risperidone, or quetiapine consistently achieve better drug therapy outcomes than patients initiating therapy using a conventional antipsychotic. The differences favoring the atypical antipsychotics are the smallest in restart episodes (13–15 days on index medication; Cox proportional HR of 0.85–0.87) and become more clinically significant when patients are switching medications (41–52 days; HR = 0.63–0.69) or augmenting an existing therapy (59–65 days; HR = 0.55–0.58).

Although olanzapine consistently displays the largest differences relative to conventional antipsychotics (26 of 32 comparisons), the range of estimated differences across the atypical antipsychotics is consistently small. For example, the difference between olanzapine and its competitors in terms of duration on the index therapy ranges from a low of 2 days for restart episodes to a high of 11 days for switching episodes.

Discussion

The differences favoring the atypical antipsychotics reported here are consistent with clinical trial results that document significantly better compliance for atypical antipsychotics when compared with conventional antipsychotics. Nevertheless, the differences favoring quetiapine and risperidone relative to typical antipsychotics are not consistent with CATIE results that found no differences between these drugs and perphenazine [2].

Our results favoring olanzapine over conventional antipsychotics are consistent with the CATIE comparisons of olanzapine with perphenazine [2]. The CATIE study found a median duration of therapy using olanzapine of 9.2 months versus 5.6 months with perphenazine in a mix of restart, delayed switching, and switching episodes. This study found the mean duration of therapy for olanzapine to vary between 4.7 months and 6.5 months, depending on episode type, compared with 3.6 to 4.3 months for conventional antipsychotics (see Table 2). Moreover, the estimated Cox proportional HR for olanzapine relative to conventional antipsychotics ranged between 0.63 and 0.85 and are consistent with CATIE results using a mix of restart, delayed switching, and switching episodes (HR = 0.78).

The results for switching episodes can be compared with phase II of CATIE in which patients switching away from their initial antipsychotic were randomly assigned to olanzapine, risperidone, quetiapine, or ziprasidone [3,4]. The CATIE results indicate that time-to-discontinuation was longer for risperidone

Table 3 Ordinary least squares models of duration of therapy using the index medication

Independent variables	Episode type			
	Restart N = 106,728 (46,836 patients)	Delayed switch N = 32,443 (24,105 patients)	Switching N = 26,024 (17,538 patients)	Augmentation N = 35,352 (19,959 patients)
Index drug (vs. typical antipsychotics)				
Olanzapine	14.54*	36.17*	52.42*	65.40*
Risperidone	12.76*	31.45*	45.84*	62.91*
Quetiapine	13.67*	28.14*	41.42*	58.56
Antipsychotic drug use history				
Change class of drugs	−2.18†	4.58‡	3.01	6.24*
Combination therapy on index date	—	17.40*	2.96	−5.12
Time off antipsychotic therapy	−0.02*	0.002	NA	NA
Duration of previous episode (in days)	0.11*	0.07*	NA	NA
Prior episodes per year	−3.55*	−1.52*	−0.12‡	−0.12‡
Prior psychotropic drug use				
Antidepressants	−2.03‡	−3.10†	−8.06*	−9.19*
Mood stabilizers	2.96‡	9.55*	6.30*	−1.27
Depot antipsychotic drug	0.58	9.42*	0.10	−9.96*
Drugs for extrapyramidal symptoms	4.60	17.11‡	−9.33	21.14*
Hypnotics	−7.97*	−3.15	−9.50‡	−4.03
Anticonvulsants	2.22†	−3.50†	0.78	−7.14*
Age (<25 as comparison group)				
Age 25–35	−0.78	2.42	−2.20	1.89
Age 35–45	−0.05	4.25	1.99	7.57‡
Age 45–55	2.86†	6.96‡	4.52	9.87*
Age 55–65	6.50*	12.02*	14.54*	10.39‡
Age 65+	9.78*	20.64*	15.91*	2.17
Race (vs. white)				
Hispanic	−0.73	−3.49	−3.43	−4.56
Black	−11.92*	−14.62*	−14.16*	−8.07*
Asian	3.98†	4.07	8.18	−4.16
Other/unknown	−4.00*	−4.28‡	−5.25‡	−2.39
Male	2.25‡	0.93	4.74§	6.87*
Prior use of health care (6 months)				
Acute hospital use	−3.11	−6.39‡	−5.05	−4.72
Psychiatric hospital use	−9.65*	−7.11*	−14.07*	−16.71*
Nursing home use	12.06*	13.28*	4.91	−22.28*
LOG_e (Total cost)	4.23*	4.86*	6.16*	3.14*
Diagnostic profile (prior 6 months)				
Infectious diseases	−6.75‡	−6.90‡	12.40†	9.22
Human immunodeficiency virus	−23.42‡	−18.87‡	−41.71‡	−20.31
Skin disorders	5.34*	3.82†	12.22*	6.50*
Muscle disorders	−4.39‡	−4.78‡	−4.82‡	−3.21†
Trauma (nonaccident-related)	−4.83*	−6.46*	−8.12*	−6.94*
Hyperlipidemia	3.98‡	1.65	10.09*	7.63*
Schizophrenia	7.05‡	3.35‡	3.24	5.93*
Anxiety	−4.70‡	−5.48‡	−12.25*	−8.97*
Depression	−1.03	−4.17†	−8.05‡	−7.58‡
Bipolar disorders	−1.41	−6.83*	−8.76*	−8.30*
Substance abuse	−10.97*	−10.91*	−14.72*	−9.51*
Dementia	16.88*	30.69*	45.73*	25.10*
Digestive disorders	−0.92	−3.41†	−5.79§	−3.59†

*$P < 0.0001$; †$P < 0.05$; ‡$P < 0.01$.

(7.0 months) than for olanzapine (6.3 months), although the HR for the likelihood of discontinuation did not confirm these unadjusted comparisons (HR = 1.02, 95% CI 0.67–1.55). Patients who switched to quetiapine achieved a median duration of 4.0 months, which was statistically shorter than for olanzapine or risperidone. Our results for duration were: risperidone 6.2 months; olanzapine 6.5 months; and quetiapine 5.5 months, with the difference between olanzapine and risperidone not achieving statistical significance.

Our results favoring atypical antipsychotics in general, and olanzapine in particular, are also consistent with previous studies using either retrospective paid claims data [7–10] or data from prospective trials designed to more closely approximate real-world clinical practice [11,12]., These previous studies, however, found larger differences between olanzapine and risperidone than reported here: 13 days in Indiana Medicaid [10]; 22 days in the US-SCAP study [11]; 29 days in Ramsey et al. [9]; 37 days in Texas Medicaid; and 44 days (unadjusted) in Michigan Medicaid [8]. These studies do not fully document the patient's prior use of nonstudy antipsychotic drugs and may therefore include a mix of long and short duration episode

Table 4 Estimated impact of atypical antipsychotics (APs) compared with conventional medications on antipsychotic medication use patterns

	Olanzapine	Risperidone	Quetiapine	Combo therapy	Changed class	Goodness of fit statistics
Restart episodes using same medication: N = 106,728* (46,836 individual patients)						
Logistic odds ratios						Pseudo R^2
Terminated index AP	0.71†	0.73†	0.72†	NA	1.01	0.1176
Terminated all APs	0.90‡	0.89‡	0.82†	NA	0.88†	0.1218
Switch/augment	0.76†	0.77†	1.15†	NA	2.10†	0.0622
Days of therapy						Adjusted R^2
Duration-index AP	15†	13†	14†	NA	–2§	0.1545
Duration-all APs	9†	8†	12†	NA	5†	0.1604
Cox hazard ratios						
Time to quit: index AP	0.85†	0.87†	0.85†	NA	1.01	
Time to quit: all APs	0.92†	0.92†	0.88†	NA	0.95†	
Time to switch/augment	0.68†	0.70†	0.97	NA	1.97†	
Delayed switching episodes: N = 32,443* (24,105 individual patients)						
Logistic odds ratios						Pseudo R^2
Terminated index AP	0.45†	0.52†	0.61†	0.80†	0.77†	0.1197
Terminated all APs	0.71†	0.75†	0.77†	0.73†	0.82†	0.1116
Switch/augment	0.73†	0.77†	0.91‡	1.43†	1.08‡	0.0495
Days of therapy						Adjusted R^2
Duration-index AP	36†	31†	28†	17†	5‡	0.1285
Duration-all APs	23†	21†	20†	20†	6†	0.1299
Cox hazard ratios						
Time to quit: index AP	0.67†	0.71†	0.72†	0.88†	0.95†	
Time to quit: all APs	0.81†	0.83†	0.82†	0.86†	0.95†	
Time to switch/augment	0.58†	0.61†	0.71†	1.11†	1.05	
Switching episodes: N = 26,024* (17,538 individual patients)						
Logistic odds ratios						Pseudo R^2
Terminated index AP	0.35†	0.38†	0.44†	1.17	0.94	0.1146
Terminated all APs	0.70†	0.70†	0.75†	0.86	0.85†	0.1019
Switch/augment	0.70†	0.77†	0.86†	1.45†	1.33†	0.0474
Days of therapy						Adjusted R^2
Duration-index AP	52†	46†	41†	3	3	0.1031
Duration-all APs	28†	27†	26†	13‡	10†	0.1041
Cox hazard ratios						
Time to quit: index AP	0.63†	0.66†	0.69†	0.95	0.98‡	
Time to quit: all APs	0.84†	0.85†	0.85†	0.87†	0.92†	
Time to switch/augment	0.60†	0.65†	0.70†	1.18†	1.28†	
Augmentation episodes: N = 36,352* (19,959 individual patients)						
Logistic odds ratios						Pseudo R^2
Terminated index AP	0.31†	0.33†	0.38†	1.09	0.91§	0.1114
Terminated all APs	0.97	0.91‡	0.95	0.95	0.86†	0.1232
Switch/augment	0.74†	0.81†	0.85†	1.50†	1.29†	0.0665
Days of therapy						Adjusted R^2
Duration-index AP	65†	63†	59†	–5	6†	0.1143
Duration-all APs	3	5§	6§	–1	10†	0.1399
Cox hazard ratios						
Time to quit: index AP	0.55†	0.56†	0.58†	0.97	0.95†	
Time to quit: all APs	0.97	0.95‡	0.95§	0.98	0.92†	
Time to switch/augment	0.76†	0.81†	0.84†	1.32†	1.19†	

*Small reductions in the sample included in the multivariate analyses were caused by missing values in one or more of the independent variables used in the models.
†$P < 0.001$; ‡$P < 0.01$; §$P < 0.05$.

types that are not equally distributed across the study drugs.

Limitations

Analyses based on paid claims data have a host of limitations that must be considered in interpreting their results. First, clinical data documenting potential differences in severity of illness and sensitivity to side effects across alternative drugs are not available on paid claims. Second, patients may not maintain continuous Medi-Cal eligibility or may receive care from other sources of coverage, such as the VA or county health facilities. However, most of the sample included in this study gained Medi-Cal eligibility because of disability status, thus reducing the likelihood of losing eligibility but increasing the likelihood of receiving care outside the Medi-Cal system. These

losses in a patient's paid claims history could bias study results if lost eligibility or out-of-system use is not equally distributed across the alternative drugs under study.

Using the gap of 15 days selected by the Medi-Cal program to define discontinuation of drug therapy can be debated. For restart episodes, which constitute nearly half of all treatment episodes, substituting an alternative gap of 30 days would collapse sequential restart episodes separated by 16 to 30 days into a single episode and increase the average duration of therapy. This change would favor the atypical antipsychotics in general, which have a smaller average gap (56–73 days, Table 1) relative to conventional antipsychotics (99 days). Moreover, changing to a 30-day gap would favor olanzapine and risperidone in particular given that these drugs are used predominately in restart episodes. Increasing the gap used to define discontinuation of therapy would have little effect on delayed switching episodes, which are separated by average gaps ranging between 236 days (typicals) and 315 days (olanzapine).

Source of financial support: This research was funded by a grant from Eli Lilly and Company, maker of olanzapine, to the University of Southern California. The University retains all rights to publication of study results subject to time-limited review and comment by Eli Lilly. Work on the research reported here was designed and conducted by the authors at the University of Southern California. Dr. McCombs served as the project's Principal Investigator. Lei Chen and Jinhee Park served as graduate research assistants' support by the research grant. Dr. McCombs has received numerous research grants from Eli Lilly and other pharmaceutical companies that market antipsychotic medications. Dr. McCombs serves on numerous technical advisor panels for these companies. Dr. Chen's current employer, Analysis Group, conducts contract research for numerous pharmaceutical companies. Jinhee Park currently works for GlaxoSmithKline.

Supplementary Material

Supplementary material for this article can be found at: http://www.ispor.org/valueinhealth_index.asp.

References

1 Croghan TW, Johnstone BM, Buesching DP, Kessler RC. Information needs for medication coverage decisions in a state Medicaid program. Med Care 1999;37(Suppl.):S24–31.
2 Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353:1209–23.
3 Stroup TS, Lieberman JA, McEvoy JP, et al. Effectiveness of olanzapine, quetiapine, risperidone and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. Am J Psychiatry 2006;163:611–22.
4 McEvoy JP, Liberman JA, Stroup TS, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry 2006;163:600–10.
5 Rosenheck RA, Leslie DL, Sindelar J, et al. Cost-effectiveness of second-generation antipsychotics and perphenazine in a randomized trial of treatment for chronic schizophrenia. Am J Psychiatry 2006;163: 2080–9.
6 Essock SM, Covell NH, Davis SM, et al. Effectiveness of switching antipsychotic medications. Am J Psychiatry 2006;163:2090–5.
7 Rascati KL, Johnsrud MT, Crismon ML, et al. Olanzapine versus risperidone in the treatment of schizophrenia: a comparison of costs among Texas Medicaik patients. Pharmacoeconomics 2003;21: 683–97.
8 Gibson PJ, Damler R, Jackson EA, et al. The impact of olanzapine, risperidone, or haloperidol on the cost of schizophrenia care in a Medicaid population. Value Health 2004;7:22–35.
9 Ramsey JL, Hutchins D, Zhu B, et al. Characteristics and treatment costs of olanzapine, risperidone or haloperidol in a state Medicaid program. Poster Presented at the Annual Meetings for the Institute on Psychiatric Services, 2002.
10 Zhao Z, Damler RM, Jackson EA, Ramsey J. Atypical antipsychotic treatment adherence and persistence in a state Medicaid program. Poster Presented at the Annual Meetings of the International. Society for Pharmacoeconomics and Outcomes Research, Arlington, VA, May 2004.
11 Swartz M, Zhu B, Ascher-Svanum H, et al. Time to all-cause discontinuation of atypical versus typical antipsychotics in the naturalistic treatment of schizophrenia. Poster presented at the International Congress on Schizophrenia Research, Savannah, GA, April 2005.
12 Haro JM, Novik D, Belger S, et al. Antipsychotic treatment discontinuation in the outpatient treatment for schizophrenia. 24-month results from the Pan-European SOHO (Schizophrenia Outpatient Health Outcomes) study. Poster presented at the International Congress on Schizophrenia Research, Savannah, GA, April 2005.
13 Choo PW, Rand CS, Inui TA, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence in antihypertensive therapy. Med Care 1999;32:1152–7.
14 Grymonpre R, Cheang M, Fraser M, et al. Validity of a prescription claims database to estimate medication adherence in older people. Med Care 2006;44: 471–7.
15 Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among

California Medicaid patients with schizophrenia. Psychiatr Serv 2004;55:886–91.
16 McCombs JS, Mulani P, Gibson JP. Open access to innovative drugs: treatment substitutions or treatment expansion? Health Care Financ Rev 2004;35:35–53.
17 White H. A heteroscedasticity-consistent matrix estimator and a direct test for heteroscedasticity. Econometrica 1980;48:817–38.
18 StataCorp. STATA 8.2. College Station, TX: StataCorp, 2004.